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Mathematical aspects of Hodgkin–Huxley neural theory

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Introduction

The work of Hodgkin and Huxley on nerve conduction has long been recognized as an outstanding scientific achievement. Their papers were published in 1952 [Hodgkin and Huxley (1952a, b, c, d)] and they received a Nobel prize in physiology for their research in 1961. Hodgkin and Huxley's work was at once a triumphant culmination of many years of theoretical and experimental work by research physiologists and a pioneering effort that set the direction and defined the goals for much of the ensuing research in biophysics.

The purpose of this book is, first, to provide an introductory description of the work of Hodgkin and Huxley and the later work that is based on the techniques that they introduced. Our main emphasis is on the theoretical aspect of the Hodgkin–Huxley work, that is, the derivation and analysis of their mathematical models (nonlinear ordinary and partial differential equations); the second purpose of this book is to describe some of the mathematics that is used to study these differential equations.

The hope is that this book will indicate to some biologists the importance of the mathematical approach and will serve as an introduction for mathematicians to the mathematical problems in the field. However, this discussion is bound to be unsatisfactory to many readers. The biologists will find the description of the physiology simplistic, crude, if not actually misleading, and they may also be dubious about the value of conclusions that can be drawn from the mathematical analysis. Mathematicians who are accustomed to the precision and stability of physics and engineering, will find the inherent uncertainty of the parameters in the models dismaying, if not disagreeable. Also, despite some very successful analysis, the mathematical problems raised by these models remain largely unsolved.

Nevertheless, this discussion is useful because it emphasizes certain questions that must be resolved in the mathematical study of biological problems. The reply to the biologist who doubts the value of mathematical techniques is that those doubts may possibly be well founded. However, it is also true that mathematical results have shed significant light on certain questions in biology. The important activity should consist not in expressing doubts, but in advancing the study of the mathematical models to the point where it can be shown clearly that they are or are not an important aspect of biological study. To the mathematician who finds the problems difficult or unattractive esthetically, the reply is even simpler. These problems are here, and criticizing their origin or aesthetic value will not make them go away.

We shall assume that the reader is familiar with basic concepts from electricity, that is, potential, current, resistance, the units in which these are measured, and Ohm's law. Since capacitance is a somewhat less elementary electrical notion and because capacitance plays a very important role in the derivation of the Hodgkin–Huxley equations, a definition and elementary discussion of capacitance have been included in the short Appendix at the end of this book.

The problem of how a nerve impulse travels along an axon has a long and interesting history. A brief summary of this history and a number of references may be found in Scott (1975). Here we shall merely point out a couple of the results that made the work of Hodgkin and Huxley possible. The membrane that surrounds the axon had been discovered and its capacitance measured by Fricke (1923). Cole (1949) had pointed out that the important quantity to be measured was the potential difference across the membrane. Equally important was the discovery by Young (1936) of the squid giant axon. The unusually large diameter of this axon (about 0.5 mm) made experimental work possible.

The work of Hodgkin and Huxley, which was a study of how a nerve impulse travels along the squid giant axon, consisted of two parts. The first was the development and application of an experimental technique called the voltage-clamp method, which was invented by Cole. By using the voltage-clamp method, Hodgkin and Huxley obtained extensive quantitative data concerning the electrical properties and activities of the axon. The second part of their work consisted in deriving a mathematical model (a four-dimensional system of nonlinear ordinary differential equations) that summarized the quantitative experimental data. They then carried out a numerical analysis of the differential equations. As will be described later, that numerical analysis showed that the differential equations were remarkably successful in predicting a wide variety of experimental results.

The work of Hodgkin and Huxley had the additional importance that it set a direction for experimental and theoretical study of other electrically active cells, that is, cells whose electrical properties change during the normal functioning of the cells. Voltage-clamp methods have been developed for the study of myelinated nerve fiber (the squid axon has a particularly simple structure and is termed an unmyelinated axon), striated muscle fiber, and two kinds of cardiac fiber. For each of these, a mathematical model has been derived by using basically the same approach as that used by Hodgkin and Huxley in their study of the squid axon.

The mathematical analysis of the Hodgkin–Huxley equations and the analogous models for other electrically active cells consists of two different parts. The first part is numerical analysis, that is, computation of approximate solutions of the differential equations. Hodgkin and Huxley themselves carried out extensive numerical analysis in their original papers and obtained the most outstanding result of the theory: the prediction of the velocity of the nerve impulse. However, as we shall see in Chapter 2, the equations can be used to predict or describe many other experimental phenomena.

Many other numerical analyses of the Hodgkin–Huxley equations have since been made, and numerical analyses, have, until now, been the most useful results for physiologists. There are, however, two serious drawbacks to numerical analysis. First, although numerical analysis can yield much useful information (as in the example of the velocity of the nerve impulse), there are many important questions that cannot be approached by use of numerical analysis. Numerical analysis cannot yield an explanation of how the potential V and the sodium and potassium currents are related. As will later be shown, the simplest and crudest qualitative analysis yields far more information of this kind. Second, numerical analysis requires the assignment of strict numerical values to the parameters that occur in the differential equations. As we shall see later, the values of the parameters, indeed the very form of certain of the functions, are not known with much accuracy. Consequently, it is important to study mathematically some class or family of equations to which the Hodgkin–Huxley equations belong, as well as to study the equations themselves.

In Chapter 2 the work of Hodgkin and Huxley is described in some detail: first the experimental work and then the derivation of the equations. It is important to see a fairly detailed description of the experimental results and their interpretation even for a reader whose primary interest is the mathematical analysis of the equations. Only a knowledge of the origin of the equations makes clear the status of the equations and the significance to physiologists of various mathematical problems concerning the equations. Chapter 2 also summarizes some of the numerical analysis that was carried out by Hodgkin and Huxley. Some of this analysis was carried out on the equatons. However, Hodgkin and Huxley also derived from this original system a system of nonlinear partial differential equations (which we will term the full Hodgkin–Huxley equations) and they carried out a numerical analysis to find traveling wave solutions of the partial differential equations. It was this analysis that yielded the prediction of the velocity of the nerve impulse.

In Chapter 3 we describe some other mathematical models of nerve conduction including various simplifications and modifications of the Hodgkin–Huxley equations. Chapter 4 describes some mathematical models of other electrically active cells that were obtained by using the basic techniques and ideas introduced by Hodgkin and Huxley.

In Chapter 5 we turn to the problem of analyzing mathematically the models that have been described. This analysis requires two quite distinct kinds of mathematics. First, we need material from the subject of ordinary differential equations including the theory of singularly perturbed equations. This material is summarized in Chapter 5. In order to study the full Hodgkin–Huxley equations, considerable material from partial differential equations, in particular the theory of reaction-diffusion equations, is needed.

Rather than attempting to present this material, we have merely described it very briefly and cited a few references. There are several reasons for emphasizing the study of the ordinary differential equations and postponing a detailed study of the partial differential equations. First, the two kinds of theory are essentially independent of one another and represent two quite different subjects. Second, the ordinary differential equations are derived directly from the experimental data and hence are closer to the real world of physiology. [Very good results are obtained from studying the full Hodgkin–Huxley equations, but it is questionable whether the corresponding partial differential equations for other electrically active cells are realistic. See McAllister, Noble, and Tsien (1975), page 4.] Finally, it seems practical to deal with the ordinary differential equations in some detail first because this will help guide future work on the partial differential equations. For example, in Chapter 6 we shall discuss the reasons why it seems strategic to regard our models as singularly perturbed systems. Moreover, by using the singularly perturbed viewpoint we will obtain useful and enlightening information about how the electrically active cells behave. If more extensive research continues to show that the singularly perturbed viewpoint is valid and informative, then it will follow that the corresponding partial differential equations should be regarded as singularly perturbed systems. But that would suggest the use of very specific theory of singularly perturbed partial differential equations rather than general reaction-diffusion theory. Thus, to some extent, the study of the partial differential equations awaits the resolution of questions concerning the ordinary differential equations.

In Chapter 6 we use the theory from Chapter 5 to study the models derived earlier. In particular, we make a detailed study of the Noble model of the cardiac Purkinje fiber. Also we summarize very briefly some of the work on traveling waves in nerve conduction, that is, traveling wave solutions of the full Hodgkin–Huxley equations.